

## REMARKS

This application pertains to novel solid lipid particles of bioactive agents and methods for the manufacture and use thereof.

Claims 1-40, 42, 44 and 45 are pending, while Claims 1-15 and 37-39 have been withdrawn from consideration as drawn to non-elected subject-matter.

The Claims under consideration are Claims 16 - 36, 40, 42, 44 and 45.

It is respectfully requested that upon allowance of claims drawn to elected subject matter the non-elected claims be rejoined.

Applicants' claims pertain to a process for producing pulverulent active substances wherein an active substance (A), initially in crystalline form, is suspended in a liquid, melted to form an emulsion and then immediately cooled to solidify the active ingredient amorphously. Further, the amorphous particles of the active ingredient are immediately coated with polyvinyl alcohol to prevent recrystallization. Applicants' process therefore provides a pulverulent active substance wherein the active substance, which was initially in crystalline form, is converted to amorphous form and preserved in that amorphous form by immediately applying a coating of polyvinyl alcohol which prevents it from reverting to crystalline form.

It is totally surprising that the active ingredient (A), which was initially in crystalline form, remains in amorphous form and does not recrystallize (paragraph [0032]). As a result of this, the bioavailability of the active ingredient remains very high (paragraph [0033]).

Those skilled in the art understand that an amorphous formulated drug is resorbed by the human body much faster than the same drug if in a crystalline state. Thus, Applicants' invention represents a tremendous advance in the state of the art!

Claims 16-36, 40, 42, 44 and 45 stand rejected under 35 U.S.C. 103(a) as obvious over Irvin (US 7,276,184) in view of Westesen et al. (US 5,885,486) and further in view of Jordan et al. (US 2002/0103285).

Applicants have previously pointed out that, contrary to their' invention, Irvin produces particles of bioactive agents which are in the crystalline form ! See, for example:

Col. 1, line 26,

Col. 5, line 16,

Col. 11, line 39,

Col. 11, line 47,

Col. 12, line 32,

Col. 16, line 10,

Col. 17, line 12m

Col. 17, line 23, and

Col. 19, line 66.

Applicants also pointed out that, Irvin specifically ***teaches away*** from Applicants' invention where, at Col. 5, line 29, he teaches that his particles are..." not in an amorphous..." form and therefore that no person reading Irving could possibly ever be led to a process wherein an active ingredient, originally in crystalline form, can be prepared as amorphous particles which are prevented from recrystallizing.

In his Response to Arguments, the Examiner seems to avoid any discussion of the fact that Irvin teaches that his particles are not in an amorphous form, and seems to dismiss this important point by simply stating that Applicants' arguments are not persuasive. Why are Applicants' argument that Irvin teaches away from an amorphous form not persuasive???

The Examiner does not in any way rebut or even attempt to rebut Applicants' argument that Irvin's product is in crystalline form and Irvin specifically teaches that his product is not in amorphous form, but instead simply expresses the proposition that "property cannot be separated from the chemistry of compound", as if this had something to do with the fact that Irvin teaches that his product is not in amorphous form.. As such, the Examiner has simply not addressed the fact that Irvin teaches away from an active ingredient in amorphous form.

The Examiner relies on Westesen for a freeze drying process (page 5, second paragraph, of the office action). As previously pointed out, no freeze drying process

could ever overcome the differences between Applicants' process for producing particles having an active ingredient in amorphous form and Irvin's process for producing particles of an active ingredient in crystalline form.

In this regard Applicants previously noted that the Examiner, at page 5 of the previous office action, referred specifically to Westesen's Example 19. However lines 52 and 53 of Westesen's Example 19 teaches that the product of his Example 19 is **recrystallized!**

Therefore, both Irvin and Westesen teach that their product is in crystallized, not amorphous form! How does the Examiner think that this teaching away from an amorphous form could possibly lead to a product in amorphous form?

Clearly, no combination of Irvin and Westesen could possibly lead to a process wherein an active ingredient, originally in crystalline form, can be prepared as amorphous particles which are prevented from recrystallizing.

When faced with these *facts*, the only comment the Examiner provides in support of his citation of Westesen is his comment on page 11 of the Office action that "...Westesen teaches active agents can be in amorphous form...". This appears to be taken out of context from the Westesen reference. At co. 9, lines 5 - 19, Westesen teaches that his solid lipid particles (SLPs) are crystalline in structure and **not amorphous** (line 9). Drugs or bioactive compounds are **entrapped into the SLPs** (col.

10, lines 20-21), and those bioactive compounds can be in crystalline or amorphous form (col. 10, lines 65-68).

However, the fact of the matter is that Westesen's SLP particles are crystalline (col. 9, lines 7-8) and such particles have the drugs or bioactive agents incorporated within them (col. 10, lines 32-33). Westesen's particles are therefore crystalline, although they can have amorphous substances incorporated within them. The particles themselves are crystalline however!

Accordingly, both Irvin's particles and Westesen's particles are crystalline and not amorphous !

The proposition that active agents can be in amorphous form does not change the fact that both Irvin's particles and Westesen's are crystalline and not amorphous.

The Examiner then turns to the Jordan reference for a dry film coating of polyvinyl alcohol. Jordan, however, applies his coatings to e.g. tablets, not to suspensions and not to amorphous suspensions of a substance that normally is in crystalline form, to prevent it from reverting back to crystalline form. Nothing in this reference teaches or suggests that a polyvinyl alcohol coating should be applied to a particle of an active ingredient, which is normally in crystalline form but which has been transformed into amorphous form, before it could recrystallize and thereby prevent it from recrystallizing. Nothing in Jordan suggests that the tablets e.g. of Jordan's Example 1 were a type that was in amorphous form, but which would recrystallize to a

crystalline form and that the coating was applied before recrystallization took place and prevented such recrystallization. Moreover, as discussed above, the Irvin/Westesens combination of references pertain to particles in crystalline (not amorphous) form. If one were to coat the Irvin/Westesens particles with Jordan's dry film coating, one would end-up with a particle in crystalline form, coated with the dry coating.

When faced with these facts the Examiner attempts to avoid the factual teachings of the Jordan reference with the statement that Jordan was quoted for teachings of coated actives with polyvinyl acetates and that the advantage that applicant has discovered due to such coating would be "obvious because property cannot be separated from the chemistry of compound" (page 9, last line of office action - page 10, 3<sup>rd</sup> line). However, the "advantage" cannot possibly be obvious because, first of all, Jordan coats a tablet, not a suspension, and second, nothing in Jordan would teach or suggest that a coating of polyvinyl alcohol can prevent an amorphous form of a substance that normally is in crystalline form from reverting back to its crystalline form.

No combination of Irvin/Westesens/Jordan could ever lead those skilled in the art to a process wherein an active ingredient, normally in crystalline form, is suspended in an aqueous phase, melted, then cooled to solidify amorphously and prevented from recrystallizing by a coating of a substance such as polyvinyl alcohol.

With regard to the showing of unexpected results in Applicants' specification, the Examiner argues that such showing is not commensurate with the scope of the instant claims. Applicants note that the Examples are all based on polyvinyl alcohol as coating

component E, and have now limited their claims to the use of polyvinyl alcohol as a coating. The showing of unexpected results are therefore now commensurate in scope with the claims.

Accordingly, Applicants' claims cannot be seen as obvious over any combination of Irvin, Westesen, and Jordan and the rejection of claims 16-36, 40, 42, 44 and 45 under 35 U.S.C. 103(a) as obvious over Irvin (US 7,276,184) in view of Westesen et al. (US 5,885,486) and further in view of Jordan et al. (US 2002/0103285) should now be withdrawn.

Finally, claim 42 stands rejected under 35 U.S.C. 103(a) as obvious over Irvin (US 7,276,184) in view of Westesen et al. (US 5,885,486), Jordan et al. (US 2002/0103285) and further in view of Rochling et al. (US 6,602,823).

The differences between Applicants' invention and anything that could be learned from the of Irvin/ Westesen/Jordan combination of references are discussed above. The Examiner relies on Rochling for specific additives. None of the additives taught by Rochling could possibly overcome the differences discussed above, however, and the rejection of claim 42 under 35 U.S.C. 103(a) as obvious over Irvin (US 7,276,184) in view of Westesen et al. (US 5,885,486), Jordan et al. (US 2002/0103285) and further in view of Rochling et al. (US 6,602,823) should now be withdrawn.

In view of the present amendments and remarks it is believed that claims 1-40, 42, 44 and 45 are now in condition for allowance. Reconsideration of said claims by

the Examiner is respectfully requested and the allowance thereof is courteously solicited.

CONDITIONAL PETITION FOR EXTENSION OF TIME

If any extension of time for this response is required, Appellants request that this be considered a petition therefor. Please charge the required petition fee to Deposit Account No. 14-1263.

ADDITIONAL FEE

Please charge any insufficiency of fee or credit any excess to Deposit Account No. 14-1263.

Respectfully submitted,  
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